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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1632	24

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/028,395	PROCKOP ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19 and 20* is/are allowed.

6)☒ Claim(s) *1-3 and 7018* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/5/01 has been entered as Paper No. 22. The Declaration of Dr. Prockop was received and entered as Paper No. 21 on 9/5/01, and the amendment accompanying the request for continued examination was received and entered as Paper No. 23 on 9/5/01. Claims 4-6 were canceled as requested. Claims 1-3 and 7-20 remain pending and are under consideration in this Office Action.

Rejections Withdrawn

After further consideration, the rejection of claims 19 and 20 under 35 USC 103 is withdrawn.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: foreign priority under 35 USC 119 is claimed, however this claim is based on PCT/US96/94497 which is not a foreign document.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for all of the reasons of record in Paper Nos. 6, 12, and 17.

The claimed invention embraces methods of treating a human patient having Parkinson's disease, stroke, cerebral ischemia, or spinal cord injury. The methods require obtaining bone marrow from a human donor, isolating marrow stromal cells (MSCs), and administering the MSCs to the central nervous system (CNS) of the patient. Prior to transplantation, the cells may

be transfected with a nucleic acid encoding a therapeutic protein which can be a cytokine, a chemokine, or a neurotropin.

As stated in Paper Nos. 6, 12, and 17, the specification is non-enabling for the claimed methods because the specification does not provide sufficient guidance as to how one of skill in the art would treat a human patient having any of the recited disorders by administering isolated stromal cells from a human donor. The specification does not disclose any disorder which has been subjected to the claimed treatment regimen, nor does the specification disclose any specific methodology associated with the treatment of any specific any disorder of the CNS. For example, the specification disclose the number of cells to be administered for each disease, disorder, or condition, the route of administration for each disease, disorder, or condition, or the relevant cell therapy target site for the specific disease, disorder, or condition in the CNS. The specification also fails to identify any specific therapeutic gene which can be used in the practice of the invention, or any specific gene/promoter combination. Finally, the state of the art at the time of filing teaches that mesenchymal stem cell transplantation and *in vivo* therapeutic effectiveness were neither routine nor predictable. For example, Prockop (Science, 276:71-74, 1997) indicates that several different strategies are being pursued for therapeutic use of MSCs, and that a phase I clinical trial demonstrated that the systemic infusion of autologous MSCs appears to be well tolerated, but also notes that "[o]bviously, however, a number of fundamental questions about MSCs still need to be resolved before they can be used for safe and effective cell and gene therapy." (see page 74, middle column). Similarly, Gerson (Nature Medicine, 5:262-

264, 1999) indicates that many questions need to be addressed regarding the utilization of MSCs in therapeutic regimens including "[w]hat is the minimal proportion of donor MSCs required to effect a long-lasting therapeutic response?"; "[w]ill transplantation of MSCs from a marrow harvest or from culture-expansion be sufficient to treat other diseases?"; "[c]an culture-expanded MSCs substitute for fresh marrow allografts in the correction of genetic disorders?"; "[t]o which host tissues do infused MSCs home, proliferate, and differentiate, and using which regulatory signals?'; "[c]an MSCs be used effectively for gene transfer and gene delivery?"; "[i]s systemic infusion optimal or is infusion into a target organ required?" (see page 264, left column).

With regard to treating central nervous system disorders using cell therapy, Sanberg et *al.* (Nucl. Acids Syrnp. Ser., 38:139-142, 1998) disclose that "[p]erhaps the most serious problem faced in the field of cell transplantation is that of a host generated immune response to the graft tissue. The prevailing strategy is to systemically immunosuppress the transplanted patient for extended periods of time. This, however, puts the patient at risk for other health problems" (see page 140, under "Issues of graft Rejection"). Sanberg *et al.* also indicate that cell transplantation has also been used to treat diseases or conditions in which neurons die, such as stroke or Huntington's Disease. As these disorders involve multiple neuron populations and extensive cell death throughout the brain, it is more difficult to treat these conditions using cell transplantation (see page 141., under "Cell Transplantation in Huntington's Disease). Thus, while the teachings indicate that mesenchymal, or marrow stromal based therapies appear to be promising, the

specific methodologies and clinical efficacy of such therapies with regard to treating central nervous system diseases remain to be established.

With regard to treating central nervous system disorders using gene Sabate *et al* (1996) caution that there are several important issues to be resolved before gene therapy for neurological diseases is to become a reality including (1) extent of transgene expression, (2) stability of transgene expression, (3) targeting of the cells, (4) safety of the procedure, and (5) vector large-scale production capacity (see page 318, left column, and in "Recombinant Adenovirus For Gene Therapy"). Sabate *et al.* indicate that the expression of adenoviral vectors persists for several months, possibly because the CNS is partially sheltered from the immune system. However, administration of recombinant adenoviruses can lead to severe inflammatory responses (see page 320, middle column, under "Future Development For Adenovirus", bridging right column). Based on the lack of guidance in the specification, it would require undue experimentation to determine which vector system, which promoter/regulatory sequence, and which nucleic acid sequence encoding a therapeutic protein should be used to transfect isolated stromal cells which are subsequently administered to a human patient to treat a disorder, disease or condition of the CNS.

Response to Arguments

Applicant's arguments, and the Declaration of Dr. Prockop, filed 9/5/01, have been fully considered but are not persuasive.

Applicant argues at pages 4-6 of the response, and pages 1 and 2 of the Declaration, that the claimed methods can be used to treat Parkinson's disease, and relies upon Schwarz et al (1999) for support. Schwarz teaches that transplantation of rat MSCs transfected with genes encoding tyrosine hydroxylase and GTP cyclohydrolase caused behavioral recovery in a rat model of Parkinson's disease. Schwarz does not provide persuasive evidence of enablement, rather Schwarz illustrates the failure of the specification to fully enable the invention and provides objective evidence of a lack of operability for the following reasons. First, the therapeutic results obtained by Schwarz are dependent on the use of both tyrosine hydroxylase and GTP cyclohydrolase expression constructs in the transplanted MSCs. However, the instant specification fails to teach or even remotely suggest the use of either of these genes. Rather the specification teaches the use of genes encoding cytokines, chemokines, or neurotrophins. See *e.g.* page 6, lines 7 and 8; and claim 10. For this reason, the teachings of Schwarz go beyond those of the instant specification, and in fact Schwarz provides critical elements, *i.e.* therapeutic genes, which are not disclosed in the specification as filed. Furthermore, and pertinent to those claim embodiments which require treatment of Parkinson's disease by administration of MSCs lacking expression constructs, Schwarz teaches that MSC transplantation in the absence of any exogenous expression construct results in no therapeutic effect. See Fig. 2, page 2543. Thus, Schwarz provides objective evidence that the specification fails to enable the treatment of Parkinson's through the use of unmodified MSCs.

Applicant argues at page 6 of the response that success in a recognized animal model correlates with a reasonable expectation of successful treatment of human disease since it is well known in the art that results obtained using such animal models are likely to be applicable to human subjects. This is unpersuasive because it lacks support. Applicant has provided no example of any treatment of any CNS disease which was developed in an animal model and which was subsequently successful in humans. For example, Applicant indicates at pages 6-7 of the response, and pages 3 and 4 of the Declaration, that Pereira (1998) and Horwitz (1999) support the position that rat models disease are predictive of human disorders, and that results in rat animal models are therefore relevant to humans. Applicant's argument is unpersuasive because Pereira and Horwitz are concerned with the treatment of osteogenesis imperfecta (OI), and not disorders of the CNS. Applicant argues that because success with MSC transplantation in animal models of OI was subsequently repeated in humans, that success in animal models of CNS disorders should also translate to success in humans. This is a gross over-simplification which completely ignores the differences between the tissues and diseases in questions. Connective and neural tissues are obviously composed of different types specialized cells with distinct structures and functions. Connective tissue cells are not required to form synapses and transmit neural impulses, any more than neurons are required to provide skeletal support. Applicant offers no support for the notion that treatments that affect OI will have any effect on Parkinson's disease or any other CNS disorder.

Applicant argues at pages 8-10 of the response, and pages 4-6 of the Declaration, that Chen (2001), Li, (2001), Olson (2001), and Chopp (2000) provide support for various embodiments of the invention. Chen teaches treatment of cerebral ischemia by intravenous administration of MSCs to a rat model of ischemia. Li teaches treatment of stroke by intracarotid administration of MSCs to a rat model. Olson fails to teach any type of therapeutic effect of any disease as a result of MSC administration. Finally, Chopp teaches treatment of spinal cord injury by direct administration of MSCs to a rat model of spinal cord injury.

At the outset, it is noted that the significance of the therapeutic results presented in Chen (2001), Li, (2001), and Chopp (2000) is unclear. Applicant's attention is directed to Figs 1 and 2 on page 1007 of Chen, Fig. 2 on page 8 of Li, and Fig. 1 on page 3003 of Chopp. These Figures report the effects on rat behavior of MSC transplantation. In all cases the standard deviation of results in transplanted animals overlaps the standard deviation of results from control animals. It is generally accepted in the art that two data sets are not significantly different when they vary by standard deviations which overlap each other. These results in animal models are relied upon by Applicant to support the enablement of claims to treatment of human disorders. In view of the tenuous significance of the results, and the fact that they were obtained in an animal model system, and not in a human, little weight can be accorded to them.

Preliminary examination of Chen and Li shows that these authors did not practice the invention as claimed or as disclosed in the specification. Chen and Li go beyond the teachings of the instant specification because Chen teaches **intravenous** delivery and Li teaches

intraarterial delivery, whereas the specification fails to teach delivery of MSCs by any vascular route. Furthermore, Li teaches that intraarterial delivery of MSC is superior to intracerebral implantation, thus the results obtained by Li are not representative of those obtainable with the claimed invention. See page 8, first sentence of third paragraph. For these reasons, Chen and Li are not analogous art and do not support enablement of the claimed invention.

Closer examination of Chen, Li, and Chopp casts further doubt on the enablement of claims 16 and 17 directed to treatment through the administration of differentiated cells. First it is noted that these publications are not analogous art for claims 16 and 17, because Chen, Li, and Chopp do not teach the delivery of differentiated cells. Second, each of these publications indicates that the likely mechanism of any therapeutic effect caused by transplanted MSCs does not involve the replacement of damaged neurons, but rather owes to the secretion by MSCs of cytokines and growth factors which promote or repair active compensatory mechanisms and endogenous stem cells within the tissue. See Chopp, page 3003, lines 17-27 of first full paragraph; Chen, paragraph bridging pages 1009 and 1010; and Li page 9 lines 14-18 of last paragraph. Furthermore, Chen teaches that it is unlikely that the observed "generation of few (~1%) BrdU-reactive cells expressing MAP-2 pf neuronal phenotype in the ischemic structures was responsible for the behavioral functional recovery observed at 14 days after [induction of ischemia]". Chen teaches that MSCs secrete a variety of interleukins, MCSF, flt-3 ligand, and stem cell factor transplanted MSCs differentiated into neurons with the proper synaptic connections to support behavioral recovery. There is no evidence of record that MSCs

differentiated as taught by the instant specification and required by claims 16 and 17 would secrete the factors which the are suspected of being required for any therapeutic effect. Thus these references do not support any therapeutic effect by transplantation of differentiated cells.

Finally, the MPEP recognizes that the physiological art is unpredictable (see MPEP 2164.03). As such, one cannot assume that results in animal models can be applied in humans, particularly in the absence of any evidence that the animal model in question has ever been used to develop any treatment which has functioned in humans. Thus, even if the results of Chen, Li, and Chopp had been obtained using the methods recited in the specification, the unpredictability of the art, as evidenced by Prockop (1997), Gerson (1999), Sanberg (1998), Sabate (1996) and MPEP 2164.03, would combine to cast a reasonable doubt as to whether the claimed invention could be practiced successfully in humans.

For these reasons the rejection is maintained.

Conclusion

Claims 19 and 20 are allowable. All claims are free of the prior art of record.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action

after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached at 703-305-6608. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Patsy Zimmerman whose telephone number is 703-308-8338.

Richard Schnizer, Ph.D.